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## CONTENTS


**Editorial:**

In Spirit and in Truth ..... 338

The Official Books of Medicinal Standards ..... 343

**Selected Editorial:**

Glass Guinea Pigs. (Reprinted From *Industrial Bulletin.*) A. D. Little, Inc., Cambridge, Mass. ..... 344

**Original Articles:**

Sterilization of Spore-bearing Bacteria in Water Supplies. By John N. McDonnell, Philadelphia, Pa. ..... 346

A Study of the Iodine Test for Toxicity in Sorghum. By R. R. Briese and James F. Couch, Washington, D. C. ..... 356

Quantitative Determination of Heroin in Mixtures of Heroin Hydrochloride and Procaine. By Charles M. Milos, New York, N. Y. .. 362

**Report of the Committee on Drug Market, Penna. Pharm. Assoc.** .... 365

**Abstracts From and Reviews of the Literature of the Sciences Supporting Public Health** ..... 370

**Solid Abstracts** ..... 388

**Book Reviews** ..... 392



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# EDITORIAL

**On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful—the editor, alone, is responsible for their type, their tone and their tenor.**

## IN SPIRIT AND IN TRUTH

THERE is a verse in the Scriptures, which, with a slight change, might well serve as the wishful, wistful prayer of every worth-while student, and serve equally well as something of a text for this brief presentation. Paraphrased, it is:

"And they that *teach* me shall *teach* me in spirit and in truth."

Regimented education in the pharmaceutical field has had a fulminating evolution. It crept upon us with much suddenness and exploded right in our faces, to some extent blinding us and deafening us, but happily, I hope, not leaving us totally dumb.

Through responsible agencies we have in part standardized our colleges and curricula, we have somehow defined our teachers, we have regulated the status though not the state of the entering and leaving student, and we have given our profession a concept of new dimensions in the field of education.

And these have been, in the main, things, safe and of happy outcome.

Yet this quantitative regimentation of education is fraught with danger to the very things it seeks to serve and save. Quantitative education is a mouth-filling phrase, but actually it is a business built of shoddy, the shoddy of thinking that education is mainly a matter of accumulating current information on current tangibles, and of knowing a little something about as many things as possible. Quantitative education brings confident ignorance. It collects tools that make for fine display, yet that rust with time for lack of knowing how and when and where to use them.

And to continue the figure, though in contrast, may I refer to a qualitative education that subscribes to the old fashioned notion that a man best keens his wits on difficulties, that considers the mind not as an ornamental set of idle tools, but as an array of useful instruments of precision, tuned and tempered to new and unfamiliar tasks, not for having known of them beforehand, but solving them as they

come with applied intelligence and plastic adaptability. Qualitative education recognizes that beauty is more practical than utility.

One of the faults of the pharmaceutical curriculum has been its confounded utility. And I insist that utility is not the yardstick wherewith the virtues, the arts, and things of sheer beauty are measured. Utility has naught to do with things of the spirit; it takes us nowhere into the ennobling terraces that afford us a glimpse beyond and away from the mundane.

Mind you, I am not advocating substituting futility for utility.

*Of course* there must be orderly laboratory work. *Of course* there must be trained teachers. *Of course* there must be painstaking instruction to the painstaking student in method, and it may be that we have to have the thesis, the theme, the purpose and the plan. But the cultural aspect of science is higher than all of these.

We too often forget that Science is ephemeral and provisional and that only Art is truly eternal.

The humanities, the classics, the æsthetics, those practical futilities, are the most changeless possessions we own. Homer has long outlasted Hannibal, and romance is older than Rome. Hymns will still be sung when the rumba and the swing will have of nature decomposed. Latin, despite its death, will yet be a vital force when many a present-day lively language is lost because of its ugly practicality.

Yes, it is the impractical phases of education that really live and lift and liberalize. These are the things that imbue a man with a sense of duty and with a consciousness of his capabilities, and, holding both as vivid trusts, make him through service and through sweat, a happiness to himself and a benediction to his brothers.

And I should love to see a good many of the so-called utilitarian subjects, with all their preening pedantry, kicked clear out of the curriculum if only I might see some of the humanities thoroughly taught in their place. Then I am quite sure that we should do away with this business of having our students wait until middle life to recover from the effects of a college education, to say nothing of relieving those who now scarcely ever recover at all.

No professor of English cherishes the mirage that his pupils will all pop into poets and shower the world with Shakespeares and Shelleys. To inculcate a love of clear beauty and of learning, and in those sequestered nooks to introduce the friendship of fine, serene old books—that is the aim of the good teacher of English.

But too many teachers in Science teach as sharpeners at the whet stone, keening the blade for instant use, and forgetting that the life and the service of the sword is more a matter of its substance and its temper.

Teaching in the sciences should not be undertaken as if we were bent on graduating jugglers of molecules and geometrists with genes. We have substituted for the leisure of the cloistered academy that terrible thing called purpose. In American educational circles today we are apt to ape the factory when we should be aspiring to cathedralated eminences.

Someone has said that those "were grand old days in Athens when Socrates with a few chosen disciples discussed in open session all things sacred and mundane. There was no class room, no heating or lighting nor need for ventilation of anything but opinion. There was no crowding, no limtiation as to subject or curriculum. No examination save the constant Socratic hammering, and no diploma, enveloping in the same smooth sheep skin one man's whole-hearted work, and another's evasion of nine-tenths of it."

But circumstances today are different—we teach a mob and not a mere handful. A horde of so-called students is taught a horde of subjects by a horde of teachers, with scarcely a Socrates amongst them all.

And who, forsooth, shall teach our teachers,—teach them to know that the real teacher must have a certain quality of guidance, persuasion and restraint that makes him capable of leading others willingly into the dominion of resourceful happiness, teach him that the essentialness of degrees is less important than the essentialness of right leadership and inspiration, that lack of breeding in teachers is more communicably toxic than the so much talked of inbreeding, that the old-fashioned idea that care of the minds of young people must be entrusted to well-trained men of gentle manners and a glorious disposition to play fair in the game of life, is still a worthy and worth-while premise.

I had occasion not so long ago to listen to a so-called teacher discourse on pharmaceutical history, and he was not qualified, either in the letter or in the spirit of the subject to inspire his young listeners, and to impress them not only with the niceties, but also with the nutrition of this far-reaching subject. What he served his class was

a desiccated fluff, and fittingly enough he qualified his own inadequacy to teach by apologizing for presenting so archaic a subject.

O Tempora! O Mores!

I subscribe to the idea that it is proper and pleasant for a teacher of pharmacognosy to interpret to his students through the medium of a tell-tale assembly of lenses the fibrovascular bundle, or the rosette aggregate of calcium oxalate crystals, but I hold it in greater stead that he has an assembly of senses wherewith to inspire his student to hear sermons in stones, to read the books in running brooks, and find the good in everything.

I subscribe to the idea of the prayer and the pedagogic practice that achieves for us our daily bread—but it is far more important to know that man may not subsist on bread alone, not even when it is buttered.

I subscribe to the idea that the modern foreign languages are a very necessary study, but I am more convinced of the need first for a more discriminate study of our own language in such a wise that we may speak it and write it, a pulsing, living thing.

It is a horror to me when I reflect over the painful illiteracy of many of our modern students and graduates in pharmacy, to say nothing of some of our so-called educators, who all too often obliterate and mangle the English of their mouths, and stutter when they put it on paper.

Is it not a concern with us that our present-day teachers in pharmacy are frequently in need, not of higher degrees, not of rarer pedagogic methodism and academic rote, but rather of those age-old essentials which are the true and permanent investments in teaching progress?

Some of us rant and rave over what we term the apathy and lethargy of our early educators and researchers, and our educational institutions. But let me say that institutions which have lasted through the decades are greater even than those men who planned them, for they take on, in growth, a spirit of their own, ceasing to be inanimate and becoming vital entities with an innate power of service and development. Let us not be too prone to criticize the old institutions just on the basis of age alone. Let us remember that the sun is old—and the moon—and even man's redeeming conscience.

I am not so certain for instance that our present regimented institutions will develop from their ranks teachers as inspiring and as

fine as those who taught the present generation of teachers: Caspari, Rusby, Chandler, Procter, Remington, Diehl, Oldberg, LaWall, Arny, Rice—and a long line of such immortals. And neither am I certain that the rigmarole of regimented educational factories will fulfill either the spiritual or temporal obligations, unless administrators and teachers alike fully recognize this fundamental twinship of spirit and of truth.

IVOR GRIFFITH.

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Z. VAMOSSY (*Orvosi hetilap*) 78:792 (Aug. 25) 1934 insists that the discovery of the laxative qualities of phenolphthalein were discovered independently by him, and not by the general public whose cheap wines had been allegedly *traced* with this bowel-disturbing drug. Quoting from the article:

"Erroneous information has been spread as to the manner in which I came upon the action of this drug. It is commonly believed that the drug was used for the denaturing of the wines made from the husks of grapes (so-called wines used by the lower classes and made by the fermentation with sugar water and pressed husks of grapes) and that after drinking of such wines, diarrhea was commonly observed. This belief is absurd for two reasons. First, phenolphthalein is pink with an alkaline solution of one to ten millions and, therefore, one hektoliter (100 liters) would need 0.01 Gm. or even 0.10 Gm. or even had they used 1. Gm. to 100 liters, it would still require for an individual to drink 10 liters of the wine to get the minimum dose to develop diarrheal action. It implies a low opinion of Hungary to believe that the government would issue regulations that might affect the public health without strict investigation. In Hungary there is established since 1876 a National Public Health Council which scrutinizes every public health measure including licenses issued by the government so that in our country even today, it is not permitted to sell chewing-gum or candy preparations containing phenolphthalein in stores dealing in groceries, delicatessens or candies. It is only permitted to be sold in packages that are regulated by law (on which the active ingredient contained in each dose is stated) in drug stores or cosmetic shops as a medicine."

## THE OFFICIAL BOOKS OF MEDICINAL STANDARDS

THE law does not insist that the preacher shall own a Bible. Indeed I often wonder whether some of them do own one. Neither has the doctor to own a medical dictionary or other work on medicine. The lawyer may have a shelf full of legislative hand books, but he is under no compulsion to have them.

Of all the professionals, the pharmacist is the only one to whom the law dictates so bookish an obligation. In most of our states he is not allowed to practice unless he actually has on the working premises, the two official books.

And I sometimes wonder whether this compulsion is a compliment or a slur. In any event, the having of them does imply the knowing of them and using of them, and since any law is fundamentally in the interest of public safety, obviously this law where it exists, tends in that direction.

Standardization of medicaments is the main purpose of these worthy books, in the formulation of which, pharmacists have played so important a part.

Our Pharmacopœia is a classic, but more than that, it is a public servant, an instrument to be dedicated to the conservation of public health. The pharmacist should know it, know it intimately. Every pharmacist should regard it as his *vade mecum,* his anchorage to professional service, his choicest contact with the medical profession, and last but not least, an authoritative standard whose sanctity he must observe not for fear of temporal law—but out of respect to his moral and spiritual obligations.

IVOR GRIFFITH.

# SELECTED EDITORIAL

## GLASS GUINEA PIGS*

DAPHNIA, favorite food for toy tropical fish, has recently leaped to scientific fame as a testing medium for medicines. The glass-like transparency of this tiny fresh-water crustacean permits clear visual observation of the effects of medicinal substances when they are dissolved in the water in which the Daphnia swims, or when they are injected into the creatures' bloodstream. It is even possible to project the image of the Daphnia under test onto a screen for group observations, and movies may be made of its reactions. So popular has the Daphnia become as a test animal that it already has competitors in the form of certain tiny transparent fish.

Anesthetics, hypnotics, alkaloids and certain toxins may be seen to act on the Daphnia heart, causing successively depressions of the beat, a stage of coupled beat, spasms, and progressively increasing rest-periods to complete paralysis or death, according to the dosage. One may observe the toxic effect being overcome by digitalis or related substances that affect the heart, in characteristic manner, as in higher animals. Caffeine increases the force of the heartbeat and slows its rate. Laxatives may be tested in 30 to 60 minutes in a remarkably quantitative manner. By Daphnia test, yeast shows up as an active laxative, and aloes, rhubarb, senna, phenolphthalein and Glauber salts also may be evaluated. Even kidney action may be observed in the nephridial bands which are analogous in action to animal kidneys.

Strychnine, in toxic doses, causes striking convulsions of the muscles of the swimming arms, and picrotoxin produces the characteristic muscular cramps noted in higher animals. Insecticides, such as rotenone, act on the respiratory organs, in this instance the "breathing legs," producing the type of paralysis which overcomes insects. Should the rotenone not be oxidized in the upper food canal, then the digestive canal will be paralyzed as has been observed in higher animals. Colored substances may be used to stain glands, to make their action easier to observe. It is possible to watch the action of poisons and their antidotes in various organs. Even metabolism studies may be made, noting the effects of temperature, drying, unbalanced diet or vitamin deficiency.

Many years ago Metchnikoff used Daphnia for studying the action of white blood corpuscles. When the creature swallowed the spores of the Monospora fungus, some of these sprouted and penetrated into the wall of its alimentary canal. Very shortly afterward, however, the white corpuscles attacked and destroyed the fungus rootlets, and thus saved the life of the Daphnia. This was a brilliant demonstration of the combined police and curative functions of white corpuscles, applicable to all animal life.

The species *Daphnia magna* has been advocated for biological service by Dr. Arno Viehoever,† who states: "Its use opens a new world for experimentation. It provides a new tool for identification and evaluation of physiologically active substances. It furnishes a unique opportunity to study the intricate mechanism and balanced rhythm of life." We are informed that important medicinal standardization is planned for the near future, with the co-operation of many prominent biologists. The physiological response of Daphnia to various biologically important materials must be correlated with that of other animals before it is used on a large scale, however. Such tests should then displace in part those now being made on higher animals such as rats, guinea pigs and rabbits, with prospect of greater accuracy and economy. Daphnia culture is well worked out so that supplies may be had at all times.

Low as is Daphnia, and simple in its appointments, it is nevertheless a complete animal with a full set of parts, each adapted to the environment. The surprising thing is that its responses to chemical and physical reagents are fundamentally the same as those of far higher and more complex creatures, due allowance being made for analogy of function of the organs under consideration. Daphnia is so far down in the scale of life that few workers will feel any compunction against its liberal use. Opportunity for the testing of medicinals, in a convenient living test tube, is now fully appreciated and plans are afoot to utilize it wherever possible.

* Reprinted from A. D. Little, Inc., *Industrial Bulletin.*

† Director of the Biologic Research Laboratories, Philadelphia College of Pharmacy and Science.

# ORIGINAL ARTICLES

## STERILIZATION OF SPORE-BEARING BACTERIA IN WATER SUPPLIES[1, 2]

By John N. McDonnell*

THE bacteriological determinations in this country which have come to be recognized as most valuable in the sanitary examination of water supplies are:

1. Bacterial count at 37 degrees C. and at 20 degrees C.
2. The finding of organisms of the B. coli group.

Many authorities ignore the significance of a high bacterial count in water, basing their sole contention for distrust of a water supply upon the content of the B. coli group of organisms, the latter being indicative of sewage contamination. The American Public Health Association standard methods, as well as other procedures, employ techniques in which lactose broth is used to detect the presence of organisms capable of fermenting the latter. Positive fermentation tests are presumptive evidence of the presence of B. coli type organisms. However, many spore-forming organisms may also cause such fermentation.

Spore-forming bacteria in water supplies have also been held responsible as agents causing some of the intestinal disturbances. Kendall[1] states that certain organisms, particularly of the spore-forming type, produce serious disturbances in the digestive and intestinal tracts of humans. This belief is also held by Gershenfeld,[2] who says that "Chronic intestinal infections have occasionally been reported as caused by these spore-bearing organisms." A statement made by some that these spore-bearing organisms are perhaps a necessary and

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[1] An abstract of a Dissertation presented to the Faculty of the Philadelphia College of Pharmacy and Science, as partial fulfillment of the requirements for the degree of Doctor of Science in Bacteriology, 1936.

[2] Research carried on in the Department of Bacteriology and Hygiene, Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania, under the direction of Dr. Louis Gershenfeld, Professor of Bacteriology and Hygiene and Head of the Department.

integral factor in the normal action of the intestinal tract has been refuted by the work of Park and Williams,[3] who in experiments in the raising of animals with sterile digestive and intestinal tracts show successfully that such flora are not a physiological necessity.

Thresh [4] states that many of the diseases of diarrhœal character are definitely known to be conveyed by drinking water.

This research was undertaken in the attempt to develop an effective and practical method of destroying, or at least reducing, the content of spore-bearing organisms in the water supplied to large communities, where the source is usually a surface water.

Incidental to this major problem, observations were made to detect the presence of spore-forming organisms in the natural sources of water supplies, that the spores are not affected by the alum treatment and pass through the filters, that they are present in samples of ordinary tap water, selected from various points in the distribution system, and that they are unaffected by the ordinary means of chlorination.

It was impossible to carry out all of many problems which present themselves in an investigation such as this. For instance, it was impossible to attempt to prove the possible injurious effects of spore-formers found in water supplies. Likewise, even in the problem of disinfection, variations (other than found in this work) in the proportions of the chlorine and ammonia might be attempted, as well as reduction in the quantity of coagulating agents added to the water, and other combinations might be considered.

In this research, water from the Belmont filter station in Fairmount Park of the City of Philadelphia was selected. Two methods of filtration, the rapid and the slow sand filtration systems, are employed there.

The media used throughout these experiments was prepared according to directions of "Standard Methods." [5] One exception must be noted. To the nutrient broth was added 5 grams of sodium chloride per litre.

## Examination of Water Supplies

The total bacterial content of the raw water entering the filter plant, and the number of spore-forming organisms, were determined.

Samples of filtered water were obtained from points in the distribution system of the city water supply. The total bacterial content of

each was estimated and characteristic spore-forming organisms isolated and identified. Anaerobic culturing was not attempted in this research.

The bacterial count of the raw water supply was approximately 4000 organisms per mil., of which 10 per cent. were spore-bearing organisms. The average number of spores in water sampled at the outlet of the sand filters was 8 per mil., a number which increased steadily as the distance traversed in the mains became greater. Characteristic spore-forming organisms found at all times in the water were identified. *B. subtilus* predominated, and in addition, *B. mycoides* was found.

## Chlorination

At the Belmont filter station, and in nearly every other large waterworks of any size or importance, some form of chlorination is practiced in addition to other treatment. Inasmuch as the average dosage of chlorine added to the water supply at the Belmont plant was found to be a maximum of 1 p. p. m., this strength and higher concentrations were employed to determine the amount of chlorine which would have a sterilizing effect upon spores.

Samples of water were prepared having a known bacterial population and subjected to chlorination. A week-old culture of *B. subtilus,* (incubated in 50 mils. of broth for forty-eight hours at 37 degrees C., and then for 5 days at 20 degrees C.) being found more resistant than a forty-eight-hour old culture, was selected for these experiments.

The first sample was subjected to a dosage of 1 p. p. m. and increasing doses were added to other experimental flasks until a point was reached where even a strength of 30 p. p. m. of chlorine had no effect upon the 20,000 organisms per mil. in the flasks. This bacterial count represented five times the total number of organisms and fifty times the number of spore-bearing bacteria found in the raw water.

Throughout all determinations in this research, controls were run on every experiment. The chlorine strength and hypochlorite content of the water in the flasks were estimated according to Treadwell and Hall.[7] A comparison of the use of ortho-toluidin color standards with the chemical titration method of estimating chlorine content showed that, for practical use, the colorimetric approximated the titration procedure, even when the water was diluted from higher strengths.

The results revealed that:

1. Chlorine up to and including strengths of 30 p. p. m. had no appreciable effect upon the spore-forming bacterial population.

2. Sufficient chlorine from the higher concentrations was carried over in the water in the dilutions for plating to inhibit growth of spores.

3. There was a noticeable drop in the strength of residual chlorine over a period of one hour. This drop approximated 20 per cent. of the original residual. Hypochlorite formation was in direct ratio to lapse of time and in inverse ratio to chlorine drop.

4. It was found advisable to have the water employed in the test exactly neutral to satisfactorily determine the hypochlorous acid content.

5. Fifty mil. broth cultures of *B. subtilus,* cultured for forty-eight hours at 37 degrees C. and for five days at 20 degrees C., were found to approximate 80,000,000 per mil.

(a) When retained at ice-box temperature, the number of bacteria per mil. in the above culture did not change.

(b) When 3 litres were prepared of this culture by diluting it to approximately 20,000 per mil., and plated in dilutions, the number per mil. varied somewhat in individual cases, but was approximately that of the apparent dilution (20,000 per mil.).

6. The bacterial content in the flasks one-half hour after chlorination approximated the original count.

7. The bacterial content in the flasks one hour after chlorination showed approximately the original count, except where an higher concentration of chlorine prevailed, and here a slight decrease of the bacterial content was recorded.

### Ammonia-Chlorination

Chlorination even in concentrations of 30 p. p. m. was found to be of no value in the disinfection of water supplies containing spore-forming organisms. The "Ammonia-Chlorine Process" (Chloramine), in which the chlorination was preceded by ammoniation, was then selected to determine its effect upon spore-bearing organisms.

In 1904, Effront [8] first suggested the use of the ammonia-chlorine process. He referred to this as nitrogen chloride. He formed the latter by the action of hypochloride on ammonia and protein in purification of drinking water. Rideal,[9] in 1910, prepared the first classic work on the possibilities of the industrial use of this process. Race [10] seems to have been the first, in 1916, to actually employ this technique in a public water supply. Then followed the works by Houston [11] and Adams [12] in England, and Paul and McAmis,[13] Spaulding,[14] and Lawrence [15] in this country. The early history of the ammonia chlorine process has been reviewed on numerous occasions by Berliner,[16] Enslow,[17] and Hinman and Beeson.[18]

The outstanding work of Montfort and Barnes,[19] in 1919, and of Harold and Ward,[20] in 1925, perfected the technique of the process, and the finally increased attention was brought to this subject by the papers of Spaulding,[22] Ruth,[23] Ellms,[24] and co-workers, notably Braidech.[25]

A survey of the literature shows that all of the work has been done solely on the problem of disinfection of water containing organisms of the colon group. I have been unable to find records of work having been done on spore-bearing organisms.

Although the early results were apparently successful, the process has until recently been used but infrequently in practice. There are two principal reasons which contributed toward this slow recognition:

1. Erratic results obtained by different investigators under varying conditions.

2. The more or less general observance that while the action of chloramine (as this ammonia-chlorine process is known) on non-spore-forming groups was more effective, its initial sterilization appeared to be somewhat delayed.

There appeared to be such a marked disagreement among the investigators of the process that some workers, notably Baker and Schmelkes,[26] deemed it necessary to correlate all available data.

In the United States, as of March, 1934, there were 650 installations of the ammonia chlorine process in operation in waterworks practice, but since conditions in the field are so varied no uniformity of practice or results may be expected in the widely separated water purification plants.

The ammonia-chlorine process is generally used for one of several purposes:

1. Prevention of after-growths.

2. Prevention of taste development.

3. Prevention of algæ.

4. Ability to carry an high residual without chlorinous odor or taste.

5. Ability to carry a residual throughout the system to protect that system from pollution, subject to chlorination, or to prevent after-growths in open reservoirs.

The activity of the chloramines has been adequately covered by Chapin,[27] Harold and Ward,[20] Holwerda,[28] Baker and Schmelkes,[26] Olszewski,[29] Braidech,[25] Dienert,[30] and others. A complete survey of the chemistry of the chloramines is given by Berliner.[16] Discussions of the problems of practical application of the process in filtration operation are given by Ellms,[24] Gerstein,[31] Enslow,[17] Jordan,[32] and other workers.

Experimental flasks of 3 litres were prepared with a bacterial content of 20,000 organisms per mil. Ammonia water (assayed according to the United States Pharmacopœia XI) was added to the flasks to produce the desired strengths in p. p. m. This was followed by the addition of three times those strengths in p. p. m. of chlorine.

The elapsed time between the ammoniation and chlorination was never less than five and did not exceed ten minutes.

Estimates of the bacterial population were made immediately after the addition of each culture and each chemical to the flasks, and after an interval of one-half hour, one hour, two hours, four hours, and six hours.

The residual chlorine was determined immediately after the addition of the chlorine and at the same intervals as above.

The results showed that:

1. Chloramine dosage of ammonia 10 p. p. m. and chlorine 30 p. p. m. yielded a sterile water in less than one-half-hour contact.

2. Dosage in decreasing amounts required increasingly longer contacts until 3⅓ p. p. m. ammonia and 10 p. p. m. chlorine

required more than one hour and less than two hours' contact to sterilize.

3. The residual chlorine showed a constant drop of 30 per cent. over a six-hour period.

4. The odor and taste of the water at the latter strengths were too strong to permit its use as a potable water.

### Alum-Ammonia-Chlorine Treatment

Experiments were undertaken to determine the effect on spore-forming organisms of the addition of a normal coagulant to the water immediately prior to ammonia-chlorine treatment. Inasmuch as alum, in quantities approximating 1 grain per gallon, is used extensively throughout waterworks practice as a coagulant in the sedimentation basins, experimental flasks were prepared, as before, and alum, in strengths of 1 grain per gallon, was added and followed within five minutes by ammonia-chlorine treatment as previously outlined. The chlorine and ammonia strengths were reduced until sterilization occurred within a four-hour period of contact. On the basis of elapsed time in the usual passage of water through the filter system, this four-hour limit represents the maximum time allowable for disinfection. At the expiration of that period it is assumed that in most filter plants the water has begun to reach the consumer and effective disinfection must have already been accomplished.

The results of the alum-ammonia-chlorine experiments were:

1. Complete disinfection of the water occurred within one-half hour, when strengths of 3⅓ p. p. m. of ammonia and 10 p. p. m. of chlorine followed the addition of alum 1 grain per gallon.

2. Reduction of the strengths of ammonia to 1⅔ p. p. m. and chlorine 5 p. p. m. showed a slight increase in time necessary for sterilization.

3. Reduction of the strengths to 1 p. p. m. of ammonia and 3 p. p. m. chlorine increased the necessary contact period to a one to two-hour period, a point most practical for application to the Belmont system. The odor and taste were not noticeable.

4. On decreasing the strengths to ½ p. p. m. of ammonia and 1½ p. p. m. chlorine with alum, sterilization was accomplished within a four-hour contact.

5. Chlorine strengths show a drop of 20 per cent. over a six-hour period.

## Conclusions

A research was conducted to determine the presence of spore-bearing bacteria in the water supplies and experimental methods of treating such water to remove all bacterial life are presented. Observations were made which revealed that:

(a) Spores of *B. subtilus* group of organisms exist in the natural sources of the water supply, a high percentage passing through the sand filters and the later chemical treatment unchanged so that they are to be found in ordinary tap water supplied by the filtration plants.

(b) Strengths of chlorine ranging up to 30 p. p. m. have no effect on spores, and that the spores develop into the vegetative forms and multiply when the chlorine content drops below the bacteriostatic level.

(c) The chloramine process (an amount of ammonia followed at a definite interval of time, by three times that amount of chlorine in p. p. m.) offers a means for disinfection for waters containing spore-bearing bacteria, and

1. that 10 p. p. m. of ammonia with 30 p. p. m. chlorine sterilizes immediately.

2. that $6\frac{2}{3}$ p. p. m. ammonia, followed by 20 p. p. m. chlorine, sterilizes within one-half hour.

3. that $3\frac{1}{3}$ p. p. m. ammonia and 10 p. p. m. chlorine sterilizes in an interval of between one and two hours.

(d) By preceding the chloramine treatment (in effective strength as given under (c)) by alum as a coagulant in strength of 1 grain per gallon, the effectiveness was increased. It was possible to reduce the ammonia strength to 1 p. p. m. followed by 3 p. p. m. of chlorine as a result of this coagulant, to produce effective disinfection in the same time and it was noted that:

1. Odor and taste at this point were not noticeable.

2. This ratio of alum, ammonia and chlorine was considered most practical for application at filter purification stations, if prechlorination is practiced with coagulants in the rapid sand filters. This ratio of chemicals, however, increased the necessary contact period to a four-hour limit.

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# A STUDY OF THE IODINE TEST FOR TOXICITY IN SORGHUM

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A RAPID test for the detection of dangerous quantities of hydrocyanic acid, or the glucoside that produces it, in cyanogenetic plants is highly desirable. At present there is available the picric acid test, which is not dependable, and a number of other color reactions of limited applicability. To obtain a definite idea of the probable toxicity of these plants it is necessary to resort to chemical analysis which is not rapid and not always possible under field conditions. Therefore when Acharya (1) describes a test with iodine in which he reported a correlation between the quantity of starch and of hydrocyanic acid in sorghum, the idea was of considerable interest to all those engaged in studying the cyanogenetic relationships in sorghum and other cyanogenetic plants. Acharya describes his procedure thus:

"The writer has, throughout the present work, found a close relationship between the accumulation of starch and that of prussic acid in poisonous *cholam,* for which no satisfactory explanation has yet been found. All plants rich in prussic acid like young *cholam* seedlings, plants stunted due to drought, second growth cholam (ratoon) and secondary shoots (referred to on p. 861), are also rich in starch in their stem, while the normal plant, after the seedling stage, is almost free from starch in the stem. This difference can therefore be utilized to distinguish between poisonous and non-poisonous plants in a simple way.

"The test is carried out by cutting a transverse section of the stem, near the bottom node, staining with iodine and examining under the microscope. Plants highly poisonous, are stained blue or black to the naked eye, and a microscope is unnecessary. Such plants generally contain above 0.1 per cent. prussic acid on the dry matter. The writer has found this relationship between starch and prussic acid to apply even at different growth periods of the same plant. In the early seedling stage, there is starch present in the stem; it decreases rapidly with vegetative growth and is almost absent at the flowering stage. It has been already noted (p. 855) how a similar variation also takes place in the amount of prussic acid present in the plant. This is a curious

relationship and can be explained either by supposing that the cyanogen compounds are combined with the starch, loosely in the 'labile prussic acid' and more firmly in the 'bound prussic acid,' or that the presence and accumulation of starch and prussic acid in the plant are both guided by the same controlling influence in the biochemical processes of the plant's life. The matter awaits further elucidation, but as it is, it can be used by the farmer as a simple and valuable test for finding out whether a particular field is poisonous to his cattle or not. He pulls up a few representative plants, takes transverse sections near the bottom node (thick sections will do), and applies a little iodine solution and observes the slide against a white background with the naked eye. If the solution is colored black or blue, the plants are dangerous and contain over 0.1 per cent. of prussic acid on the dry matter. If there be no apparent staining, the slide may be observed under the microscope. If there be a good many starch grains visible, stained blue or black, gathered especially round the xylem vessels, the plants contain prussic acid, but not to a dangerous extent (below 0.1 per cent.) ; whereas, if the section is fairly clear, the cattle can be fed on the field without any fear. After a few hours' practice, any farmer can learn to do the above testing for himself."

The test as proposed is a starch reaction, and since previous knowledge of the tide of nitrile-glucoside formation made it appear that this was not likely to be parallel with that of starch formation, it was desirable that the iodine test be examined carefully for dependability.

An opportunity presented itself during the season of 1937. Weekly collections of a number of varieties of sorghums were being made at seven localities and the hydrocyanic acid content of each sample was being determined. Application of the iodine reaction to these samples would constitute a fair test of the method with accidental circumstances excluded to a great extent.

The samples were collected and the test applied by the following collaborators. At the same time samples were preserved in 1 per cent. mercuric chloride and shipped to the laboratory at Washington, D. C., for analysis, and other samples were taken for moisture determinations. All figures cited in this paper refer to the hydrocyanic acid content in mg. per 100 g. calculated to dry plant. The collaborators were J. H. Martin, Bureau of Plant Industry; J. J. Curtis, who furnished samples grown at the United States Experiment Station,

Akron, Colorado; J. C. Stephens, Bureau of Plant Industry, Experiment Station, Chillicothe, Texas; B. F. Barnes, United States Dry Land Field Station, Delhart, Texas; A. F. Swanson, Fort Hays Experiment Station, Hays, Kansas; D. B. Burnham, United States Dry Land Field Station, Tucumcari, New Mexico, and J. B. Sieglinger, Southern Great Plains Field Station, Woodward, Oklahoma. Samples from the Bureau of Plant Industry Experiment Station Farm at Arlington, Virginia, were collected by the writers. The varieties represented in the samples were:

| | |
|---|---|
| Feterita, | Western Blackhull kafir, |
| Sumac sorgo, | Finney milo, |
| Hegari, | Leoti sorgo, |
| Dwarf Yellow milo, | Honey sorgo, |
| Texas Blackhull kafir, | Dakota Amber sorgo, |
| Dawn kafir, | Dakota Amber (Sel. 39-30), |
| Sharon Blackhull kafir, | Sudan grass, |
| Sedan Red kafir, | Johnson grass. |

Samples of hegari, Sudan grass and Johnson grass were taken from whole plant except that at Hays hegari was taken as whole plant until the final leaf appeared and then leaves only were collected. With the other varieties the plan, as described for Hays, was followed at the other stations. Since animals will graze leaves in preference to stalks, the procedure gives a better indication of the quantity of hydrocyanic acid cattle will be likely to get than if the whole plant is sampled especially when the stalk is large and tough. The probability of poisoning therefore can be decided more accurately from data on the leaf than on the whole plant.

The results of the tests are presented in Table 1. The observers were asked to indicate the comparative depth of the color produced by the iodine, and the results necessarily varied with the personal equation of the various individuals making the test. In the report from Akron all of the samples gave at least a faint test and none were reported "deep." At the other stations a considerable number of samples were reported "none" or negative.

Tests were made at intervals on the samples collected at the Experimental Farm, Arlington, Virginia. The hydrocyanic acid content of these samples varied from 265 mg. per cent. in young plants to

8.2 mg. per cent. in leaves from mature plants in October. In no case was a positive test obtained with any of these specimens. The Arlington plants were grown under conditions where there was an abundant supply of water available throughout the growing season. This may have influenced the rate of starch formation.

The figures presented in Table 1 are averages of 625 collections segregated to show the number reacting in each way at each station

TABLE 1

RESULTS OF TESTS OF SORGHUM SAMPLES. HYDROCYANIC ACID REPORTED IN mg. % OF DRY PLANT

| Station | | Color | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | Negative | Faint | Slight | Medium | Deep | |
| Akron, Colo. | Number of Tests | | 13 | 31 | 10 | | 54 |
| | Maximum HCN | | 284 | 268 | 232 | | |
| | Minimum HCN | | 43 | 64 | 35 | | |
| | Average HCN | | 137.4 | 180.5 | 127.8 | | |
| Chillicothe, Tex. | Number of Tests | 17 | | 57 | 40 | 19 | 133 |
| | Maximum HCN | 237 | | 287 | 287 | 352 | |
| | Minimum HCN | 23 | | 10 | 18 | 19 | |
| | Average HCN | 130.1 | | 73.9 | 102.6 | 78.5 | |
| Delhart, Tex. | Number of Tests | 26 | 17 | 61 | 26 | 25 | 155 |
| | Maximum HCN | 361 | 361 | 358 | 232 | 271 | |
| | Minimum HCN | 7 | 19 | 7 | 9 | 17 | |
| | Average HCN | 161.4 | 186.2 | 144.9 | 138.6 | 104.8 | |
| Hays, Kan. | Number of Tests | 26 | | 27 | 1 | 9 | 63 |
| | Maximum HCN | 415 | | 426 | 192 | 328 | |
| | Minimum HCN | 74 | | 16 | | 145 | |
| | Average HCN | 170.8 | | 199.8 | 192 | 221.6 | |
| Tucumcari, N. M. | Number of Tests | 46 | | 18 | 17 | 16 | 97 |
| | Maximum HCN | 281 | | 219 | 192 | 146 | |
| | Minimum HCN | 11 | | 49 | 33 | 18 | |
| | Average HCN | 132.1 | | 106.1 | 111.4 | 69.8 | |
| Woodward, Okla. | Number of Tests | 26 | | 43 | | 54 | 123 |
| | Maximum HCN | 210 | | 210 | | 263 | |
| | Minimum HCN | 5 | | 5 | | 7 | |
| | Average HCN | 87.6 | | 66.2 | | 57.6 | |
| Totals & Averages | Number of Tests | 141 | 30 | 237 | 94 | 123 | 625 |
| | Maximum HCN of all | 415 | 361 | 426 | 287 | 352 | |
| | Minimum HCN of all | 5 | 19 | 5 | 9 | 7 | |
| | Average HCN of all | 136.4 | 161.8 | 128.5 | 120.1* | 106.4 | |

*Excludes Hays.

with the maximum, minimum and average hydrocyanic acid content of each type. The data indicate that the quantity of hydrocyanic acid which may be obtained from the plant bears no relation to the depth of color produced in the iodine test. Young plants were uniformly negative according to the standard of Acharya and yet these contained the greater portion of hydrocyanic acid. Older plants in which the content of hydrocyanic acid was well below a lethal limit gave positive reactions. As shown in Table 2, over 50 per cent. of those giving a

TABLE 2

NUMBER DEFINITELY NON-LETHAL, HCN LESS THAN 60 mg. %

| Station | Color | | | | |
|---|---|---|---|---|---|
| | Negative | Faint | Slight | Medium | Deep |
| Akron, Colo. | | 3 | 0 | 1 | |
| Chillicothe, Tex. | 2 | | 34 | 11 | 11 |
| Dellfart, Tex. | 7 | 3 | 7 | 4 | 7 |
| Hays, Kan. | 0 | | 1 | | 0 |
| Tucumcari, N. M. | 4 | | 4 | 3 | 8 |
| Woodward, Okla. | 4 | | 23 | | 37 |
| Totals | 17 | 6 | 69 | 19 | 63 |

"deep" color and over 20 per cent. of those giving a "medium" color were below the lethal limit. Of those samples that gave no color, 87.94 per cent. were above a lethal limit, while 80 per cent. of those reported "faint" and 70.88 per cent. of those reported "slight" were also above the lethal limit. The lethal limit was set at a figure of 60 mg. per cent. on a dry basis as a result of feeding tests and may be somewhat high. The majority of animals receiving sorghum material of this concentration will be fatally poisoned.

In a number of cases tests made on five to six stalks at the same time showed a variation, some being negative while others gave a more or less distinct color. At several times during the season the observer applied the test to other parts of the plant and found evidence of starch toward the tips, in the branches, and base of leaves when the lower node gave none or a slight test only.

Tests applied to second growth plants showed none or slight reactions except for one sample of hegari at Hays, which gave a deep color and contained 324.4 mg. per cent. of HCN. At the same time a

sample of feterita which contained 393.3 mg. per cent. gave a negative reaction.

Regarding the general averages of all the tests, it appears that the highest average HCN content relates to the group that gave a faint test. Next in order of HCN content is the group that gave no test. The groups that gave slight and medium tests follow in order, while the group that gave the most pronounced test and therefore should have been the most toxic gave the smallest average HCN content of the five. Of the negative group, thirty-one samples contained over 200 mg. per cent. of HCN.

It appears evident, therefore, that under the conditions of these tests there is no correlation between the quantity of starch and hydrocyanic acid in sorghum.

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# QUANTITATIVE DETERMINATION OF HEROIN IN MIXTURES OF HEROIN HYDROCHLORIDE AND PROCAINE

By Charles M. Milos†

PROCAINE is sometimes used as an adulterant for heroin. Its presence does not alter the color tests generally employed in the qualitative identification of heroin. When present in large amounts crystalline tests generally used in the identification of heroin are modified in varying degrees.

The presence of procaine is indicated by the purple color produced by its reaction with furfural. The reagent used is as follows:

| | |
|---|---|
| Freshly Distilled Furfural | 2½ cc. |
| Alcohol | 22½ cc. |
| Glacial Acetic Acid | 75 cc. |

(J. A. Sanchez: A Color Reaction of Cyclic Primary Amines. *Anales. Assoc. quim. Argentina 23,* 431 (1925), *C. A.* 20, 2300. A Test for Recognition of Primary Cyclic Amines. *Ann. Chim. Anal. Chim. Appl. 14,* 132 (1932), *C. A.* 26, 3070.)

The following method makes use of the fact that when procaine is hydrolized in acid solution, one of the resulting products; para aminobenzoic acid is not extracted from an ammoniacal solution to any extent by chloroform containing 10 per cent. of alcohol and the other resulting product; diethyl amino ethanol is insoluble in lime water, whereas morphine resulting from the hydrolysis of heroin is extracted from an ammoniacal solution by chloroform containing 10 per cent. of alcohol and is soluble in lime water. The presence of sugar of milk, sucrose, and quinine do not alter the final results.

## Method

Take 0.5 to 0.8 gram of a representative sample and transfer to a 250 cc. Erlenmeyer flask. Add 50 cc. of approximately normal sulphuric acid, and reflux for 45 minutes, or boil on a hot plate for 45 minutes, adding a little water from time to time as the volume diminishes, then concentrate to a volume of 25 cc. After cooling transfer to

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separator No. 1, washing the Erlenmeyer flask twice with 5 cc. of water. Now add 5 cc. of 95 per cent. ethyl alcohol and 10 grams of sodium chloride, then shake until salt has dissolved. Make the solution ammoniacal with concentrated ammonia, adding a few drops in excess, shake out five times with chloroform containing 10 per cent. of alcohol, using 30-20-20-10 and 10 cc. respectively. Filter each shake out into separator No. 2. Discard the liquid in separator No. 1.

To separator No. 2 add 25 cc. of lime water (U. S. P.), shake and withdraw the chloroform into separator No. 3. Add 15 cc. of lime water to separator No. 3, shake and withdraw the chloroform into separator No. 4, adding the lime water in separator No. 3 to separator No. 2. To separator No. 4 add 10 cc. of lime water, shake and reject the chloroform and save the lime water. Take the lime water in separator No. 2 and shake it twice with 20 cc. of choloroform, collecting the chloroform in separator No. 4. After shaking separator No. 4, discard the chloroform and after making the lime water acid with concentrated hydrochloric acid, add it to separator No. 2.

Now add concentrated hydrochloric acid to separator No. 2, until acid, then add 4 to 5 drops in excess. Add 5 cc. of alcohol and 15 grams of salt, then shake until the salt has dissolved. Make ammoniacal with strong ammonia, adding a few drops in excess, and shake out five times with chloroform containing 10 per cent. of alcohol, using 30-20-10-10 and 5 cc. portions, filtering each into evaporating dish.

Evaporate off the chloroform on a steam bath. Dissolve the residue, which is morphine and should be white, in 5 to 10 cc. of methanol and add an excess of N/100 sulphuric acid and 2 drops of methyl red. Heat on a steam batl for ½ hour, and if no undissolved specks are visible, cool and back titrate with N/100 sodium hydroxide. Each cubic centimeter of acid = .00369 gram of anhydrous heroin.

## Experimental Results

In determining the accuracy of this method a good grade of heroin hydrochloride was mixed with varying quantities of procaine hydrochloride. The per cent. of anhydrous heroin in the heroin hydrochloride used in all the experiments was found by the method given in the A. O. A. C., page 566, fourth edition 1935, to be 80.2 per cent. When pure procaine hydrochloride was also run by this method, the final residue gave no color reaction with the furfural reagent and no crystals with platinic chloride.

In the following table all samples were run by this method.

| No. | Grams Heroin HCl: | Grams Procaine: | Grams Milk Sugar: | Calculated % of Anh. Heroin: | Actual % of Anh. Heroin Obtained: | Final Residue in grams: |
|---|---|---|---|---|---|---|
| 1 | | 0.35 | | | | .0006 |
| 2 | | 0.50 | | | | .0010 |
| 3 | 0.1120 | | | | 78.8 | |
| 4 | 0.1272 | 0.0410 | 1.3328 | 6.8 | 6.5 | |
| 5 | 0.1012 | 0.1778 | | 29.1 | 28.9 | |
| 6 | 0.1119 | 0.0270 | | 64.6 | 63.8 | |
| 7 | 0.1152 | 0.0333 | | 62.2 | 62.1 | |
| 8 | 0.1400 | | | | 78.5 | |
| 9 | 0.0953 | 0.0657 | 0.5771 | 10.36 | 10.15 | |

## Conclusions

1. A method is given for the quantitative determination of heroin in the presence of procaine.

2. The presence of sugar of milk, sucrose, and quinine do not interfere.

3. The morphine formed by the hydrolysis of heroin serves as an added confirmatory test for heroin.

4. The presence of any substance insoluble in lime water will not interfere with the method.

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# REPORT OF THE COMMITTEE ON DRUG MARKET TO THE ANNUAL CONVENTION OF THE PENNSYLVANIA PHARMACEUTICAL ASSOCIATION

## At Wilkes-Barre, Pa., June 13-16, 1938

IN accordance with our usual custom of reporting as extensively as possible on the quality of pharmaceutical raw materials, your committee has studied the data submitted by the various laboratories contributing to our report. The gratifying condition noted during recent years has again been maintained; in fact, one laboratory reported that it was necessary to reject only 37 of the 3781 samples examined.

Our survey this year showed that several lots of volatile and fixed oils were of unsatisfactory quality. Two samples of oil of lavender failed to comply with the U. S. P. requirements for specific gravity and solubility in 70 per cent. alcohol. Three shipments of oil of turpentine were rejected because they were contaminated by a foreign substance. This condition has been noted at various times with other articles, and in this case was caused by the condition of the containers. One sample of redistilled oil of peppermint was not satisfactory in odor and did not comply with the U. S. P. solubility test. Oil of lemon domestic did not meet the U. S. P. refractive index requirement and the solubility test. One sample of oil of rosemary was also not of U. S. P. quality. Three samples of cottonseed oil were rejected because they did not comply with certain private tests requiring an oil for specific purposes, having a purity greater than the U. S. P. requirements, particularly in regard to color and congealing point. One importation of cod liver oil contained considerable sediment and did not pass the U. S. P. test for destearinated cod liver oil. This lot was received in drums and apparently had become cloudy during unfavorable storage conditions.

Among the chemicals, we found that a shipment of citric acid contained water-insoluble substances, and berberine bisulfate an excess of water-soluble substances. Sodium phosphate contained an excess of heavy metals, arsenous iodide contained free iodine, and sodium bromide contained bromates. Magnesium oxide, potassium bromide and precipitated manganese oxide were also not of satisfactory quality. Solution of sodium glycerophosphate had an objectionable odor.

One shipment of colchicine contained an excess of water. It was quite evident that this lot had not been properly purified. Three samples of caramel offered were not of N. F. quality, one shipment was low in tinctorial value. Several samples of liquid petrolatum were unsatisfactory because of odor and an excess of paraffins. A similar condition to that found with oil of turpentine was found with liquid styrax, which had a gasoline odor, and 20 degrees ammonia water which contained an excessive amount of sediment. Both of these undesirable conditions were traced to the condition of the containers.

Other unacceptable conditions were noted in synthetic menthol, which had an abnormal odor; vanillin with an improper melting point; powdered saffron contaminated with foreign substances; podophyllin with an excess of moisture; liquid guaiacol which had an objectionable odor, and soft soap which was not of U. S. P. quality.

The following data submitted by W. J. Bott gives an interesting account of the quality of crude drugs particularly in regard to moisture and packaging requirements for digitalis and ergot;

The quality of imported crude botanical drugs has been vastly improved over that which was supplied to the American market many years ago. Deliberate adulterations today are negligible, because of careful inspection at various ports by the United States Department of Agriculture. Many of the regulations are rather stringent and often not in line with "Mother Nature"; in such cases, research and cooperation with the responsible authorities has been effective in creating revisions of the original specifications.

Years ago, gum benzoin, for instance, reached this market decidedly "false packed" with dross material, but this has been overcome, and today most shipments of gum benzoin pass all requirements rather regularly. With the advent of the U. S. Pharmacopœia, 11th Revision a specification announcing rosin as an adulterant in gum benzoin made imporation of this article rather difficult. Rosin appears in gum benzoin almost as a natural consequence, since it is a natural constituent and never appears as a deliberate adulteration. It is present to the extent of not more than 1 per cent. to 1½ per cent. Crude drug importers, foreign shippers and their agents, and various associations, combined in presenting the facts to the proper pharmacopœial committee, and eventually a revision was made ignoring the rosin specification.

Also, the moisture test on aloes, as well as the purity test, created quite a disturbance, but here again is a case that could hardly be called deliberate adulteration. Curacao aloes comes from one of the most primitive points of the world, and as in the case of gum benzoin, there is found a certain amount of natural impurities. These impurities enter when the gum is "tapped" from the trees, and cannot be avoided. The primitive source of the material makes it impossible to create any facilities for the refining of the crude article, which must be done after the importers receive the crude material.

The moisture content of gentian root and gum arabic are easily affected by atmospheric conditions. Gum arabic, for instance, is gathered in the Sudan during the rainy period of May, June and July. In view of the primitive condition under which this type of drug is produced, it is readily seen that proper drying is a very difficult problem. In the case of gentian root, for instance, it has been observed by various importers that, although a shipment is received in a bone dry condition, it will, if allowed to remain on a well-covered dock during forty-eight hours of rain, absorb enough moisture to run above the 10 per cent. tolerance. If the shipment is sampled immediately following this period and the sample placed in an air-tight container, it is evident that the result obtained will not represent the shipment when received. It is evident then that a condition has arisen which was beyond the control of the foreign shipper, the importer, or the U. S. Department of Agriculture. If this shipment is taken to the importer's warehouse in this excessively moist condition, it will dry during storage without any damage or deterioration, and meet the moisture tolerance. Here, again, cooperation and research among those interested effected a revision in moisture standards of gum arabic and gentian root so that today we have no difficulty in importing them.

Digitalis and ergot were very badly affected by the packing requirements and moisture tests as required by the 11th Revision of the Pharmacopœia. No revision has yet been possible in this case despite the continued barrage of criticism by foreign shippers, the New York importers, and various associations. Digitalis has become practically impossible to import because of the packing requirements, which require that digitalis be shipped in air-tight, moisture-proof containers. The purpose of these requirements is to prevent the digitalis from absorbing moisture during transportation to this country,

as it is considered that the excessive moisture in most shipments of digitalis is responsible for the variance in the assay.

Digitalis, no matter how well cured abroad and no matter how well treated in artificial drying methods, will never run better than 10 per cent. moisture. While it may be artificially dried in such a way that it will contain but 6 per cent. of moisture, it will on a rainy day, for instance, absorb as much as 2 per cent., 4 per cent., 6 per cent. and 8 per cent. of moisture in as many hours between the time it is dried and then packed in the air-tight moisture-proof containers. The same may be said of ergot. This effect has been shown to exist by actual scientific research study.

The difficulty is that the storing of digitalis and ergot in moisture-proof air-tight containers even when they contain the permissible amount of moisture, subjects them to the action of mould particularly when stored during transit in the hold of a vessel or in a warehouse. Various importers and manufacturers have found this to be an actual fact. Mould will spread in such packing, and all agree that the former method of shipping digitalis and ergot in loose-pressed, clean burlap bags was far more satisfactory, since any excess moisture would dry out naturally through the ventilated burlap bags during storage in the hold of the vessel, and seldom arrive here containing more than 8 per cent. moisture. Most digitalis and ergot that reaches here cannot be used in the crude form. It must be either granulated for percolation to make it ready for subsequent manufacturing in extracts, or it may be powdered for pill and capsule work. The carefully controlled milling operation will drive out in a natural way all the moisture that is in excess of the 8 per cent. tolerance. It has been done in this way for many years without difficulty.

Digitalis when excessively heated in an attempt to artificially dry the article and take out the excessive moisture, is often affected in biological activity. Therefore, when a foreign supplier meets one specification, his shipment may be turned down on arrival for not being in conformity with the biological activity test. Ergot, however, in all fairness to everyone concerned has met both the moisture and packing specifications more readily than digitalis. It is believed by importers and manufacturers that the air-tight, moisture-proof packing should be discarded, and a revision effected in the moisture requirements.

Seeds like anise, fennel and coriander have in the past caused much trouble in respect to the presence of excessive foreign matter, and of rodent excreta, but this again is not adulteration, as rodent excreta can contaminate the seed while en route in the hold of the vessel, and upon arrival is detected and the shipment subsequently detained by the Department of Agriculture. The U. S. Department of Agriculture after being informed of the unfairness of the condition consented to the reconditioning of such importations on arrival. The general practice is to allow these shipments to be thoroughly cleaned by licensed Government reconditioners.

The committee wishes to extend thanks to the staffs of the laboratories of Sharp & Dohme, S. B. Penick & Company, and Smith, Kline & French for the material submitted in this report.

GEORGE F. APPLIN,
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MARTIN KOVACS,
JAMES C. MUNCH,
EDWARD C. REIF,
J. MERVIN ROSENBERGER,
J. G. ROBERTS, *Chairman.*

# ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

Bacteriology . . . . Louis Gershenfeld, B. Sc., Ph M.
Biochemistry, Nutrition, etc. . . . Arno Viehoever, Ph. D.
Biology . . . . . Marin S. Dunn, Ph. D.
Chemistry . . . . . Arthur Osol, Ph. D.
Pharmacy . . . . . E. Fullerton Cook, Ph. M.
and their assistants

## NEWER PHARMACOLOGY OF THE EPINEPHRINE HOMOLOGUES*

By Horatio C. Wood, Jr., M. D.

THE autonomic nerves, which regulate the activity of the vital organs, are divided into two groups, both by their anatomical relations and by their reactions to drugs. One group, arising in the brain, passes through the skull to be distributed to the various organs; the other runs from the spinal cord through the chain of ganglia which lie on either side of the cord and are known as the "sympathetic" ganglia. The latter group of nerves are called the sympathetics, the first are known as the parasympathetics.

Among the multifarious effects of stimulating the sympathetic nerves may be mentioned, as of especial interest to the pharmacologist, dilatation of the pupil of the eye, contraction of the arteries, relaxation of the bronchial and intestinal muscles, increased contraction of the heart and augmented discharge of glycogen from the liver. It will be noted that some of these effects are in the direction of increased functional activity (excitor) and others lead to lessening of the organic functions (inhibitory).

The term "sympathomimetic" is applied to those drugs which cause effects more or less comparable to the results of stimulating the sympathetic nerves. The best known of these drugs are epinephrine

*The first of a series of articles by Dr. H. C. Wood, Professor of Pharmacology at the College, Co-editor of the United States Dispensatory and an outstanding authority in the fields of pharmacology and materia medica.—*Ed.*

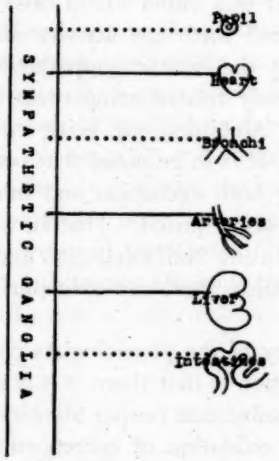



DIAGRAM TO ILLUSTRATE ORGANS SUPPLIED BY THE SYMPATHETIC NERVES.
Solid Lines Indicate Excitor Nerves.
Dotted Lines Indicate Inhibitory Nerves.

and ephedrine, but recently a number of synthetic compounds of somewhat similar actions have been introduced into medicine. There are important differences between the actions of epinephrine and ephedrine, as well as those of the newer synthetics which will be pointed out.

The chief therapeutic uses of these drugs, based on these actions, are: (1) To contract the arteries locally for the purpose of overcoming congestions as in rhinitis, or to stop hemorrhage, or to prevent the absorption of local anesthetics; (2) To increase the blood pressure in various forms of circulatory failure; (3) To relax the bronchi in asthmatic states; (4) To overcome various allergic manifestations as urticaria, hay-fever, etc.; (5) To overcome severe forms of intestinal spasm.

In 1931 Cannon found that after prolonged excitation of the sympathetic nerves there could be extracted from the arterial muscles a substance which, when injected into another animal, would cause the characteristic changes that follow stimulation of the sympathetic nerves. To this substance he gave the name of "sympathin," but it is now believed to be identical with epinephrine. For this reason the term "adrenergic" is now being used to replace the older one sym-

pathomimetic. Later it was found that a dose of epinephrine which was large enough to call forth the activity of the inhibitory group would not affect equally the excitor sympathetics. It is now believed that there are two closely related compounds formed by stimulating the sympathetics; the inhibitory one being epinephrine, the excitor being nor-epinephrine. It is to be noted that both of these compounds are capable of causing both excitation and inhibition, the difference being in the relative doses required. That is, that while both of these drugs are capable of causing both excitation and inhibition the former is predominantly inhibitory and nor-epinephrine predominantly excitor.

The present theory of the physiologists concerning the response to sympathetic stimulation is that there is contained in the nerve endings of these nerves a substance (either identical with or closely allied to the product of the oxidation of epinephrine); when an impulse, either nervous or electrical, passes down the nerve this material is reduced to active epinephrine (or some nearly related compound) which causes the appropriate response in the muscle supplied. The epinephrine then undergoes rapid oxidation losing its physiological power, the shortness of the response to sympathetic stimulation being due to the rapidity with which it is oxidized by the bodily tissues.

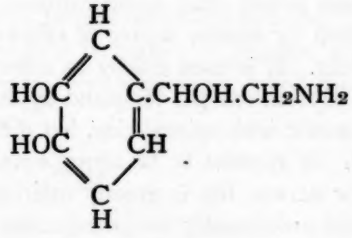
### The Newer Adrenergic Compounds

While the researches into the fundamental physiological problems involved in the action of these drugs have been going on another group of investigators have been studing the relationships of chemical structure to physiological effect. These latter studies have led, in the last two or three years to the introduction, for clinical use, of a number of new synthetic compounds more or less resembling epinephrine in their actions. While many of these have as yet not been sufficiently studied to permit of accurate evaluation of their therapeutic value, the pharmacological studies which have been made afford grounds for at least a tentative judgment of their probable value.

From the standpoint of chemical structure these adrenergic drugs may be divided into three groups, as follows: (1) those having two hydroxyls in the phenol ring (hydroquinones), those having one hydroxyl (phenols) and those having none (benzyls).

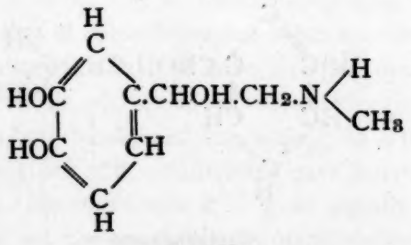
The first group includes epinephrine, nor-epinephrine (arterenol), epinine and cobefrine. They are characterized by showing both

the inhibitory and excitor effects of sympathetic stimulation and by being very rapid and fugacious in their actions. The fugaciousness of the effects of this group is readily understandable when we recognize that the destruction of epinephrine in the body is an oxidative one; from the presence of two hydroxyls we should naturally expect these compounds to be easily oxidized. Tainter and his coworkers have laid considerable stress on the fact that they give a well-marked ergot reversal and are potentiated by the previous injection of cocaine. The ergot reversal test means that if an animal has received previously one of the ergot alkaloids the injection of the sympathetic stimulant will cause a fall, instead of a rise in the blood pressure.



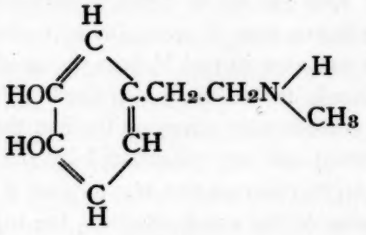

**Epinephrine**

Nor-epinephrine as far as I know is not commercially available in this country for clinical use, but is being used in Germany under the name of arterenol. It differs in chemical structure from epinephrine only in the lack of one methyl radical. It is approximately equal to epinephrine in its effect on the excitor nerves, but its action on the inhibitory nerves is less potent than epinephrine, although still considerable.




**Nor-epinephrine**

Epinine differs from epinephrine in its chemical structure by lacking a hydroxyl in the ethane side-group.

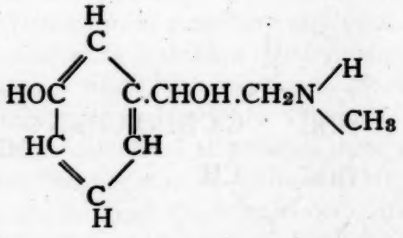


Epinine

It is considerably less potent than epinephrine—requiring about 10 times the concentration for similar degree of effect—and is somewhat slower and less violent. It is used chiefly as a local vaso-constrictor usually in strengths of from one per thousand up to one percent.

Cobefrine is isomeric with epinephrine, but differs in the position of the $CH_3$ radical. It appears to be about equal to epinine in its action on the excitor nerves, but is greatly inferior in the inhibitory effects. It stands out prominently for two reasons: first, because of slow and enduring action (it is the only one of this division which causes obvious effects when swallowed) and secondly, because of its strong stimulating action on the heart. It does not appear to possess any advantage as a local vaso-constrictor or as a bronchial relaxor, but may prove of real clinical importance in the treatment of surgical shock and other forms of acute circulatory failure.

The only one of the phenolic division of any practical importance is neosynephrine.

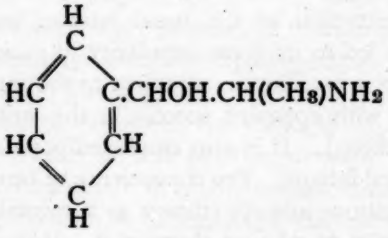


Neosynephrine

This substance is relatively potent in its effect on the arteries, but is much less powerful in its inhibitory actions, as for the relief of asthma. Its action is rather fleeting, although slightly more prolonged than that of epinephrine. It is said to have the great practical advantage of being more stable in solution. It is widely employed by laryngologists as a local vaso-constrictor in strengths from ¼ to 1 per cent.

The third group—with no hydroxyl in the nuclear ring—includes ephedrine, benzedrine and propadrine. Ephedrine is so well known that it is scarcely needed to discuss its uses except to point out that it has one property which is not common to the adrenergic drugs, that of exciting cerebral function. As a result of this effect it sometimes gives rise to wakefulness even after local applications and is used to overcome the sense of fatigue instead of caffeine,

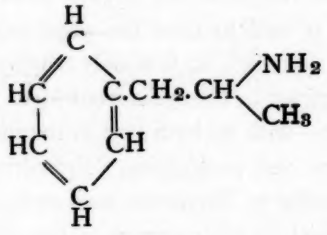
Propadrine (which is known in Europe as nor-ephedrine and mydriatine) differs in structure from ephedrine in the lack of one $CH_3$ group.




**Propadrine**

It occurs naturally in certain species of Ephedra, but is chiefly made synthetically. According to Tainter its pressor dose is about 60 times as big as that of epinephrine and it has no relaxing effect on the bronchi (inhibitory action). I have seen but one report of its clinical use, that of Black, who used it in various allergic states as hay-fever, asthma, etc., both locally and internally. As a topical application he employed a 1 per cent. solution and gave internally from 1/3 to 2/3 of a grain. He states that it is about equally efficient with ephedrine and does not cause wakefulness or nervousness.

Benzedrine differs chemically from ephedrine in lacking a methyl and an hydroxyl group.




Benzedrine

Physically it is unique among the series in the fact that it is volatile. In its effects on the arteries it is weaker even than ephedrine and like that drug is comparatively slow in its action. On the inhibitory division is has relatively little effect, Tainter finding that it is of no value as a relaxant of the bronchi, but it has been used clinically in intestinal spasm. Because of its volatility it is possible to obtain local vaso-constriction of the nasal mucosa merely by inhalation, which fact has led to its great popularity in various forms of coryza. Like ephedrine it is an active stimulant to the intellectual centers and is being used with apparent success in the treatment of narcolepsy (pathological sleep). It is also employed popularly to overcome the results of mental fatigue. The convenience of benzedrine for the relief of nasal congestions and its efficacy as a mental stimulant creates a strong temptation to popular abuse of it. It must be borne in mind that it is capable of much harm, not merely by depriving persons of needed rest but, probably, also by inducing an injurious elevation of blood-pressure. Benzedrine may be applied locally, dissolved in liquid petrolatum, in strengths of 1 per cent.; for internal use the sulfate may be given in doses of one-twentieth to one-eighth of a grain.

# RECENT INVESTIGATIONS ON THE PNEUMOCOCCUS AND PNEUMONIA

By Louis Gershenfeld, Ph. M., B. Sc., P. D.
Professor of Bacteriology and Hygiene, Philadelphia College of Pharmacy and Science, Philadelphia, Pa.

**Recent Advances in the Treatment of Pneumonia.** H. C. Hinshaw. *Proceedings of the Staff Meetings of the Mayo Clinic 13,* 369 (1938). All physicians who treat pneumonia should be familiar with several developments which are destined to alter the management of this disease. The following are emphasized: (1) Classification of pneumococci into at least thirty-two serologically specific types, (2) development of the Neufeld method of rapid, direct typing of pneumococci in sputum, (3) production of effective therapeutic sera which soon will be available for use against several additional types of pneumonia, (4) use of rabbits for the production of therapeutic sera, and (5) use of sulfanilamide and related compounds in treatment.

Serum therapy is available only for cases of pneumonia caused by the pneumococcus. The great majority of cases of lobar pneumonia, a considerable percentage of cases of bronchopneumonia, and an undetermined percentage of cases of postoperative pneumonia are caused by pneumococci. The time has arrived when every reasonable effort should be made to determine the etiologic organism in every case of pneumonia at the earliest possible moment. Bacteriologic study of the sputum need not await roentgenologic confirmation of the diagnosis. In urgent cases, a bacteriologic diagnosis can be made within an hour or less. It is absolutely necessary that the type of pneumococcus be determined, because serum is of no significant value except against its homologous type of organism. The specimen submitted for bacteriologic examination must represent exudate expectorated from the lung and it should be examined promptly. It is necessary to instruct both the patient and nurse clearly about the importance of submitting a suitable specimen for examination. Sometimes it is necessary to examine more than a single specimen. Blood should be obtained for culture in every case of lobar pneumonia on admission to the hospital and sometimes this procedure should be repeated. Therapeutic approach is greatly modified and the prognosis gravely affected by the presence of a bacteremia. Serum is the only effective treatment for bacteremia and the mortality rate continues high in spite of such

treatment. It is stated that the newer types of rabbit serum are administered somewhat differently from horse serum and that the usual cutaneous and ophthalmic tests are somewhat less reliable. Rabbit serum is prone to produce an early febrile reaction, but usually this is not serious except among patients who have an unusually high fever. It is possible to administer rabbit serum more rapidly, in larger amounts, and in fewer doses than horse serum. The effectiveness of serum therapy is multiplied by early administration and many of the apparent failures are directly attributable to late treatment. For this reason it is rarely permissible to withhold serum because of mild initial symptoms. There is no dependable method of forecasting the eventful severity of the disease at the onset. The error of delay may permit extension of the disease to other lobes and possibly bacteremia or complications with greatly increased cost and hazard. When serum therapy is delayed until the fourth day or later, the amount of serum required is much greater and in an effort to conserve the patient's financial resources he may be subjected to increased expense. The apparent high cost of serum is mentioned constantly as a reason for withholding it from patients. When the actual value of serum is realized, this objection vanishes. At present prices, adequate, early, serum therapy costs no more than two or three days of oxygen therapy with continuous private nursing service. Actually, it is possible for serum therapy to save expense by shortening the period of hospitalization, by decreasing costs of oxygen therapy and of special nursing and by preventing extremely expensive complications such as empyema. The effectiveness of modern serum therapy in cases of pneumonia no longer can be a subject for debate. When adequate doses are administered on the first or second day of the disease, it will lead frequently to prompt termination of the disease by crisis. It has long been proved that the mortality associated with pneumococcus pneumonia may be halved by serum therapy. It is now hoped that even more striking results may be realized with newer methods.

Sulfanilamide has not only definite pneumococcidal properties but also definite dangers when used in treatment of this disease. Its tendency to alter the hemoglobin of the blood may seriously hamper the already overtaxed capacity of the blood for carrying oxygen. Instances have been observed in which repeated transfusions were required to restore destroyed hemoglobin. Undoubtedly, sulfanilamide must be used more cautiously in cases of pneumonia than in cases of

other types of disease. It is possible that it has a place in the treatment of pneumonia, but its limitations and indications must be determined accurately.

Pneumonia continues to be capricious and a deadly disease. The amount of skill and judgment required is increased rather than decreased by the newer methods of approach to its treatment. The literature on the subject is growing rapidly and there are remaining differences of opinion, but the principles stated above are agreed on by the authorities who have had the greatest experience with the treatment of pneumonia.

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**A Study of the Diagnosis and Treatment of Lobar Pneumonia According to Types and Specific Serum Therapy.** Julien E. Benjamin, Marion Blankehorn, James M. Rugesegger and Fannie A. Senior. *Ann. International Med. 11,* 437 (1937). Four hundred and eighty-five cases of lobar pneumonia observed during the sixteen-month interval were typed. Of these, 66 per cent. were either type I, II, V, VII, VIII, XIV, XVIII, for which serum was available. Of the 66 per cent., 139 were admited within ninety-six hours of onset and were given intravenous injections of serum. Those admitted later than ninety-six hours after onset, and of the types for which serum was not available, were not given serum therapy. The mortality in the 485 cases was 25.15 per cent. as against 30 to 50 per cent. over a period of six years prior to the use of serum. For the 73 serum-treated type I not treated with serum: For the other types, treated and untreated, the mortalities were: II, 30.7 and 34.6 per cent.; V, 18.1 and 30.5 per cent.; VII, 0 and 24 per cent.; VIII, 0 and 13.6 per cent.; XIV, 0 and 75 per cent.; XVIII, 0 and 20 per cent. The unsatisfactory results with type II serum were attributed to insufficient dosage.

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**Serum Therapy of Pneumococcic Pneumonia.** Rufus I. Cole. *J. Am. Med. Assoc. 109,* 2059 (1937). More than 500 cases of type I pneumonia were treated with immune serum with uniformly satisfactory results. The mortality was under 4.8 per cent. for patients treated in the first three days, 8 per cent. for those treated on the fourth day, 8.6 on the fifth day, and 19.5 on the sixth day. In the last 51 cases of type I pneumonia treated with concentrated horse

serum and rabbit serum, not one of the patients died. The need for larger doses of serum is emphasized. Type II serum gives less satisfactory results in type II pneumonia than type I serum in type II cases. With types V, VII, VIII, and VI pneumonia, the disease is not as severe and the specific serum is given in smaller doses. Only few severe anaphylactic reactions develop. Most reactions are promptly controlled by epinephrine. Serum sickness is never serious and may be disregarded when compared to the life-saving effect of the serum.

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**The Management of Pneumonia.** Jessie G. M. Bullowa. *J. Am. Med. Assoc. 109,* 2061 (1937).

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**A Study of Type I Pneumococcus Epidemic at the State Hospital at Worcester, Mass.** Warnock, White and Smillie. *Am. J. Public Health 3,* 293 (1938). Sixty-seven pneumonia type I pneumococcus patients and a carrier prevalence of at least 200 of type I pneumococcus were found in the institution during the epidemic. The fatality rate of the epidemic was high, despite extensive use of the type I anti-pneumococcus serum.

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**The Modern Treatment of Pneumonia.** Evert A. Bancker. *J. A. M. Alabama 7,* 218 (1938).

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**Problem of Chemotherapy in Pneumonia.** W. W. G. Maclachlan. *Sci. Monthly 45,* 105 (1937). Clinical trials reveal that hydroxyethylapocupreine is compatible with all forms of serum which may be used in specific type pneumococcus infections.

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**Serum Therapy in Lobar Pneumonia.** W. H. Potts. *Texas State J. Med. 33,* 418 (1937).

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**Treatment of Type VII Pneumonia With Serum.** Pneumonia Editor. *New York State J. Med. 38,* 33 (1938).

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**Course and Treatment of Lobar Pneumonia.** R. Haberkorn. *Münch. med. Wochschr. 84,* 1934 (1937).

**Modern Trends in the Diagnosis and Medical Treatment of Lobar Pneumonia.** N. I. Nissen. *J. Am. Med. Assoc. 109,* 1322 (1937).

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**Pneumonia Studies: II. Serum Treatment of Croupous Pneumonia.** N. I. Nissen. *J. Am. Med. Assoc. 109,* 1322 (1937).

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**The Serum Treatment of Pneumococcus Lobar Pneumonia.** C. N. Hensel. *Minnesota Med. 20,* 658 (1937).

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**The Serum Treatment of Pneumonia.** J. Natt. *Virginia M. Monthly 64,* 267 (1937).

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**Lobar Pneumonia. Etiologic Diagnosis and Specific Treatment.** J. D. Dowling and George A. Denison. *J. M. A. Alabama 7,* 212 (1937).

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**Lobar Pneumonia in Children. Differentiation of Recovered Pneumococci Into Etiologic Groups and Their Familial Distribution.** Elizabeth T. Andrews. *Am. J. Diseases Children 54,* 1285 (1937).

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**Possibilities for Penumonia Control as Indicated by Present Scientific Knowledge.** R. Cole. *Military Surgeon 81,* 241 (1937).

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**Pneumonia From the Standpoint of Preventive Medicine.** John H. Mehrling. *New York J. Med. 37,* 1827 (1937).

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**The Treatment of Pneumonia With Deuterproteose.** C. Brooks. *South M. J. 31,* 534 (1938). A series of 1787 cases of all forms of pneumonia were divided into two groups: one group received 2-3 cc. of a 10 per cent. aqueous solution of deuterproteose twice daily by intramuscular or intravenous injection. The other group served as a control. The treated cases recovered with a marked but gradual downward trend of the temperature and other clinical signs, including the blood count, blood sedimentation rate, as well as pulse, respiration and general condition of well-being of the patient.

**Prophylaxis and Therapy of Postoperative Pneumonia.** E. Plaas. *Deut. Med. Wochschr. 63,* 1768 (1937). It was found possible to prevent postoperative pneumonia and other pulmonary conditions by the administration of anastil-calcium, composed of guaiacol and calcium glutinate.

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**The Occurrence of Different Types of Pneumococci in Cases of Acute Pneumonia in Stockholm.** S. Gard, G. Lofstrom and G. Jacobson. *Acta Med. Scand. 95,* 483 (1938).

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**Pneumococcus Septicemia Complicating Peritonsillar Abscess With Specific Serum Therapy.** James J. V. Cammisa. *U. S. Naval Med. Bull. 35,* 339 (1937).

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**Properties of the Type Specific Proteins of Antipneumococcic Sera. I. The Mouse Protective Value of Type I Sera With Reference to the Precipitin Content.** Kenneth Goodner and Frank L. Horsfall, Jr. *J. Exptl. Med. 66,* 413 (1937).

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**Properties of the Type Specific Proteins of Antipneumococcus Sera. II. Immunological Fractionation of Type I Antipneumococcus Horse Serum and Rabbit Sera.** K. Goodner and F. L. Horsfall, Jr. *J. Exptl. Med. 66* (1937).

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**The Response of Infants to Inoculation With Type I Pneumococcus Carbohydrates.** John A. V. David. *J. Immunol. 33,* 1 (1937). Fifteen infants from two to fifteen months of age were inoculated subcutaneously and intracutaneously with type I pneumococcus carbohydrate. Only one responded with demonstrable humoral type I pneumococcic antibody.

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**Effect of a Heat-resistant Enzyme Upon the Antigenicity of Pneumococci.** Rene J. Dubos and Colin M. Macleod. *Proc. Soc. Exptl. Biol. Med. 36,* 696 (1937).

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**The Specific Capsular Polysaccharide of Pneumococcus Type I and the Immunity Which It Induces in Mice.** Allan W. Downie. *J. Path. Bact. 45,* 131 (1937). Immunity induced in mice by pneumococcus polysaccharides was type-specific and was passively transferred to normal mice.

**Experiments With Type-specific Pneumococcus Polysaccharides in Rabbits.** Allan W. Downie. *J. Path. Bact. 45,* 149 (1937). Two preparations of the specific polysaccharide of type I pneumococcus did not reveal antigenic activity on repeated injection into normal or immunized rabbits.

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**Chemo-immunological Studies on the Soluble Specific Substance of Pneumococcus. III. The Structure of the Aldobionic Acid From the Type III Polysaccharide.** Rollin D. Hotchkiss and Walter F. Goebel. *J. Biol. Chem. 121,* 195 (1937). The aldobionic acid from the specific capsular polysaccharides of types III and VIII pneumococcus has been shown to be glucose-4-B-glucuronide.

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**Prophylactic Vaccination Against Intracranial Complications Following Pneumococcus Type III Mastoiditis.** Jos. L. Goldman and Cecele Herschberger. *J. Am. Med. Assoc. 109,* 1254 1937.

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**Pneumococcus Typing in the Public Health Laboratory.** Wallace B. McClure. *Can. Med. Assoc. Jr. 38,* 365 (1938).

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**The Characteristics of Antipneumococcus Sera Produced by Various Animal Species.** F. L. Horsfall, Jr. *J. Bact. 35,* 207 (1938).

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**The Chemotherapy of Pneumococcus Infections.** B. Kemkes. *Klin. Wochschr. 16,* 1041 (1937).

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**Pneumonia Due to Type V Pneumococcus.** M. B. Rosenblith and M. Block. *Arch. Internal Med. 60,* 567 (1937). Three and five-tenths per cent. of 1850 cases of pneumococcic pneumonia observed during the past eight years were type V. The mortality rate in 39 cases of serum-treated type V pneumococcus pneumonia was 26 per cent. compared with 29 per cent. type V cases not treated with serum.

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**The Globulin Fractions of Antipneumococcus Serum.** Arda A. Green. *J. Biol. Chem. 123,* 44 (1938).

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**"Difficulties Encountered in Pneumococcal Type Determination."** Walter. *Am. M. Pub. Health 1,* 54 (1938). Specimens for

pneumococcal type determination should be fresh and should not contain a disinfectant. Peritoneal exudate may best be typed by the Neufeld method. Rabbit serum for the Neufeld reaction should be tested against all types and only specific serum should be used.

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**An Intracutaneous Rabbit Test for the Assay of Antipneumococcus Serum.** J. Ipsen, Jr. *J. Path. Bact. 46,* 571 (1938).

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**Lipoid Pneumonia and Oil in the Lungs (Review).** *J. Am. Med. Assoc. 109,* 1376 (1937).

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**Experimental Bases for Serotherapy of Pneumonia.** F. Neufeld. *Deut. med. Wochschr. 64,* 219 (1938).

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**Complications in Pneumonia.** Philadelphia County Med. Soc. Pneumonia Committee. *Weekly Roster and Med. Digest 33,* 849 (1938). Complications seldom occur in patients treated with antipneumococcus serum which results in a cure in the course of the pneumonia. Patients treated late in the disease after complications have begun may reveal an increase in the incidence of complications by the use of serum. Horse serum has no curative influence on any of the common focal purulent complications during the lobar pneumonia. Rabbit serum, which supposedly has greater penetrating power for serous membranes is still to be proven to be more effective in this respect.

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**Further Experiments on the Effect of Certain Quinine Derivatives on the Pneumococcus.** John M. Johnston, H. B. Burchell, H. H. Permer and W. W. G. Maclachlan. *J. Pharmacy 61,* 364 (1937).

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**The Effect of the Bacteriolytic Enzyme of Pneumococcus Upon the Antigenicity of Encapsulated Pneumococci.** Rene J. Dubos. *J. Exptl. Med. 66,* 113 (1937).

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**Mechanism of the Lyasis of Pneumococci by Freezing, Thawing, Bile and Other Agents.** Rene J. Dubos. *J. Exptl. Med. Assoc. 37,* 18 (1937).

**Properties of the Type Specific Proteins of Antipneumococcus Sera. III. Immunochemical Fractionation of Type I Antipneumococcus Horse and Rabbit Serum.** Kenneth Goodner and Frank L. Horsfall, Jr. *J. Exptl. Med. 66* 437 (1937).

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**Parenteral Protein in Pneumonias.** Clyde Brooks. *Arch. Path. 23,* 744 (1937). In 1200 cases of all forms of pneumonia one-half of the patients were used as controls and the other half was treated by the parenteral administration of deuterproteose. The results indicate that the parenteral use of deuterproteose reduces the death rates of both lobar and bronchial pneumonia.

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**Community Provision for the Serum Treatment of Pneumococcic Pneumonia. Report of the Committee on Public Health Relations of the New York Academy of Medicine by a Special Sub-Committee.** R. L. Cecil, J. G. M. Bullowa, H. T. Chickering and E. H. L. Crowin. *Bull. New York Acad. Med. 13,* 457 (1937). Pneumonia statistics, pneumonia control, and serum production are presented. Pneumococcus types vary from year to year, making it difficult for health laboratories to have available adequate amounts of different type serums. Type I pneumococcus is most prevalent. Types III, VII and VIII held second place at different occasions.

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**Cinchona Alkaloids in Pneumonia. V. Alkyl Ethers of Apocupreine.** C. L. Butler, M. Hostler and L. H. Gretcher. *J. Am. Chem. Soc. 59,* 2354 (1937). Ethers of apocupreine were prepared by alkylation of apocupreine with the appropriate alkyl p-toluenesulfonate. All possessed strong action against the pneumococcus and mouse toxicity higher than that of ethylapocupreine. The unmodified apocupreine ethers in general appear not to be suitable for trial in human pneumonia.

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**The Treatment of Pneumococcic Infection With Camphor and Other Terpenes.** E. Berger and F. Koepplin. *Klin. Wochschr. 16,* 1147 (1937). Subcutaneous administration of d-camphor, borneol, bornyl acetate, and camphene possesses a prophylactic action on pneumococcic type III in white mice. Inactive camphor and terpineol have no effect.

**The Biology of Pneumococcus.** E. White and Collaborators. *The Commonwealth Fund,* New York (1938). This interesting and valuable work covering approximately 800 pages is a review of the literature on the biology of the pneumococcus forming part of the Pneumonia Study and Service carried on during the years 1931 to 1935 by the Massachusetts Department of Public Health under a grant from the Commonwealth Fund. The chapters consider the following phases: History of the pneumococcus (30 pages); biology of the pneumomoccus (35 pages); biochemical features (38 pages); classification of pneumococci (30 pages); pneumococcal dissociation and transformation (45 pages); pathogenicity of pneumococcus experimental animals (35 pages); pathogenicity of pneumococcus, man (24 pages); chemical constituents of pneumococcus (63 pages); specific polysaccharide-splitting enzymes (22 pages); antigenicity of pneumococcus (32 pages); antibodies to pneumococcus (72 pages); host response to antigenic action of pneumococcus (52 pages); pneumococcal vaccines (28 pages); chemotherapy (15 pages); production of antipneumococcic serum (76 pages); serum treatment of lobar pneumonia (15 pages); unsolved problems (10 pages). There then follows an appendix on special methods used in the study of pneumococcus and in the preparation of antipneumococcic serum (43 pages) and a bibliography (106 pages).

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**Use of Mice for Testing Toxicity of Rabbit Therapeutic Antipneumococcic Serum.** Kenneth L. Burdon and Edward L. Burns. *Proc. Soc. Exptl. Biol. Med. 38,* 343 (1938). Mice proved more uniform than rabbits as test animals for the toxicity of rabbit antipneumococcic serum.

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**Non-specific Measures in the Treatment of Pneumonia.** Charles G. Gormly. *Rhode Island M. J. 21,* 87 (1938).

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**Antigenic Activity of Extracts of Pneumococci.** Allan W. Downie. *J. Hyg. 38,* 279 (1938). Unfiltered extracts of pneumococcus type I (prepared by extracting bacterial cells with .05 N HCl) gave active immunity in mice and rabbits and specific antibodies were produced in their sera. Filtrates were antigenic in mice due undoubtedly to the presence of type-specific polysaccharide, but they possessed no action in rabbits, the antigenicity in these animals being due to the

pneumococcal cells. The addition of 66 per cent. alcohol produced preparations which were not antigenic in the rabbit.

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**Pneumococcus Antitoxin.** G. F. Dick and A. K. Boor. *Arch. Path. 26,* 93 (1938).

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**Pneumococcus Polysaccharide in Urine.** Current Comment. *J. A. M. A. 110,* 2158 (1938). Urinary excretion of the specific capsular substances formed by pneumococci is of little or no diagnostic value, owing to the inconstant excretion of this substance during the early stages of lobar pneumonia. Cruickshank, of the University and Royal Infirmary, Glasgow, Scotland, however, believes that detection of the type-specific polysaccharide in the urine is a valuable prognostic index, the mortality among patients with "pneumococcosuria" being twenty times greater than that of pneumonia patients whose urine remains free from this polysaccharide during the course of the disease. Cruickshank's conclusions were drawn from his study of about 200 patients with pneumococcic infections, 184 of whom were suffering from lobar pneumonia. Type polysaccharides were estimated quantitatively in the urines of these patients by means of high titer type-specific antiserums. The serum used in most of his tests was capable of detecting homologous pneumococcus polysaccharide in dilutions as high as 1 : 5,000,000. The daily output of type pneumococcose in some of his cases was as high as from 3 to 30 mg. The mortality of his patients with type I or II polysaccharide excretion was about 40 per cent. The saccharide-free urines was only 2 per cent. In a certain number of cases with delayed resolution the specific polysaccharide continued to be excreted for from twenty-five to forty days during convalescence, presumably as a result of the gradual dissociation of humoral or intracellular antibodies. Whether or not urinary excretion of pneumococcus specific substance is a physiologic process or a pathologic process due to toxic injury to the kidney epithelium has not been determined. If, however, pneumococcosuria is a reliable prognostic index as Cruickshank believes, it may be a valuable guide to a rational therapy in lobar pneumonia. Cruickshank suggests that specific serum therapy should be limited to patients with positive pneumococcus polysaccharide in the urine.

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**Use of Polyvalent Antipneumococcus Serum, Kyes.** W. E. Cary. *Arch. Path. 26,* 147 (1938).

# SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

**Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.**

It is a strange commentary on the vagaries of the usually alert Yankee that he suffers long and meekly when a little well-applied organization might ease his hurt and stop his worry. Consider the hayfeverite. Ninety per cent. of the sneezing, snorting polinotics who put the gust in August are victims of the rugged ragweed. The breezes that bear the pollen love of one weed to another, are during that season, laden with this toxic treason that swills its poison through the victim's system.

With no ragweed around, ninety per cent. of our hayfever would vanish, a great portion of our populace would be more pleasant to live with, much unneeded noise would cease, and perhaps we might all act more sensibly at election time.

And why should this weed not be eliminated exactly as we seek to eliminate the Cannabis? Why should not an army of unemployed be turned loose on this obnoxious enemy? As a matter of fact poison ivy and the ragweeds might well, by concentrated action, be eradicated or at least, held to such a minimal spread, as to bring to many a present worried victim some slight surcease from his woe.

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*And speaking of pollen grains listen to this bit of up-in-the-air research.*

*Hayfever pollen grains fly high, Oren C. Durham, botanist of the Abbott Laboratories, discovered in the course of a week's research cruise back and forth across the ragweed belt in transport planes of the United Air Lines. But despite the presence of pollen in the air outside, passengers within the big cabin planes were safe from sneezes. The pollen concentration inside was practically zero.*

*Pollen ceilings had previously been reported as varying from 3000 to 4000 feet. In this survey the ceiling was found to vary from*

*4800 to 9000 feet above the ground. Heavy concentrations of pollen were found over northern Ohio and Indiana up to about 6000 feet. Small amounts of pollen were found in eastern Colorado as high as 9000 feet above the ground. Definite pollen ceilings were found to be marked by cloud layers, whether these layers were continuous or merely consisted of numerous cumulus clouds.*

*In perfectly clear skies there seems to be no well marked level at which pollen contamination stops. Rain interfered considerably with the study, clearing the air of pollen at certain low levels and hindering exposures part of the time.*

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Wilson said "The knowledge of words is the gate of scholarship," and so that this gate may be opened a mere more, here are two brand new words. You can add them to your vocabulary on the introduction of Dr. Edward Teller of George Washington University in Washington, D. C.

Listening to a new explanation of the old phenomenon of phosphorescence, scientists attending a Stanford University summer conference on photochemistry, heard the words "exciton" and "phonon" as new descriptive terms applied to subatomic particles whose behavior under certain conditions produces phosphorescence.

Light may excite two kinds of energy when it strikes a solid body, Dr. Teller believes. It may excite electronic energy, the moving particle thus resulting from the impact of the light being defined by the scientists as an "exciton." A particle vibrating from the other type of excitation for which he holds light responsible Dr. Teller calls a "phonon."

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*I remember my amino-acid largely because my old professor of chemistry used to joke about the COHN linkage that cleft itself in amphoteric twain when a water wedge became inserted. He called it "hydrolysis." But amino acids have until recently given way to vitamins in dietary dominance. Now they come back.*

*For thirty years the relationship of these amino acids to growth has been studied, but since 1930 there has been an extensive push in the laboratory at the University of Illinois presided over by Professor W. C. Rose.*

*Until recently there were only three of these compounds that had been shown to be indispensable components of food. Their names were tryptophane, lysine and histidine. Now through patient animal experimentation with foods whose protein content consists of carefully purified amino acids of various kinds, Dr. Rose and his co-workers have a list of ten amino acids finally classified as "essential to growth." They are in addition to the three previously so cataloged: phenylalanine, leucine, isoleucine, threonine, methionine, valine, and arginine.*

*Dr. Rose classes the other 12 of the known 22 amino acids as non-essentials so far as growth is concerned. Among them is cystine, one of the better-known amino acids, which previously was widely considered an indispensable component of food.*

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Whether you are underweight of overweight, and even though your heart is in the right place, you are doing it damage. Excess weight gives the heart too much work. If you are underweight, on the other hand, the heart beat and the circulation are slowed, your heart shrinks in size and you are more liable to serious complications following minor infections and injuries and you are what is called a poor surgical risk.

The importance of diet in relation to the heart was recently pointed out by Dr. Louis A. M. Krause, of the University of Maryland, in an address under the auspices of the Baltimore City Health Department and the Medical and Chirurgical Faculty of Maryland.

"In the past," Dr. Krause said, "heart and blood-vessel disease was thought to be due solely to the changes caused by germs, or by developmental defects. Of late we have learned that nutrition is a problem of primary importance and, in many instances, that improper nourishment results in defective heart action. It may be that the faulty nutrition permits the entry of some disease germs."

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*And to continue this heart-to-heart talk do you know that the average adult's heart pumps about six quarts of blood every minute, or 2000 gallons every day. Someone has figured that there are five miles of blood vessels in every pound of fat. So you can see how*

*much extra work you are giving your heart with every pound of surplus weight.*

*It is the fatty foods and the sweets that add on the surplus weight, it appears, except in cases of glandular disorders. An excess of vegetables or animal protein (meat) apparently never causes heart or blood-vessel disease.*

*So watch your calories, and intake them, if you can, according to the gospel of "just enough."*

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Devotees of the lawn mower may soon spend their devotion elsehow, for it is predicted that grass as lawn upholstery is about to be superseded by a less bothersome nap. Chamomile lawns are a favorite for bowling greens in England because they are very resilient and stand well the wear of walking feet. A few plants spread out in a lawn will drive grass out, so vigorous is chamomile's growth. Thyme occasionally has been used as a lawn plant and yarrow likewise. In California *Lippia* is sometimes used.

But the lawn plant *par excellence* is the small turfing daisy, *Matricaria tchihatchewi,* which ought to make life easier for the man of the house. This plant gives a thick green foliage never more than two inches high. It does not need watering, will grow almost anywhere except in deep shade or very sandy soil and requires no more than one cutting a year.

# BOOK REVIEWS

**Done by persons, unafraid to upbraid, but perfectly willing to give praise where praise is really due.**

**A Textbook of Biochemistry.** Roger J. Williams. D. Van Nostrand Company, Inc., New York, N. Y., 1938. 525 pages, including index, and 40 tables. Price: $4.00.

This book has admittedly been written for medical students and others similarly interested in animal biochemistry. Thus a detailed discussion of plant and agricultural, as well as industrial, biochemistry should not be expected in this latest work by Williams, who is also the author of "Introduction to Biochemistry," a book published in 1931.

His object has been to present not a storeroom of facts, meaningful or not, but material, carefully selected and arranged like a planned exhibit. In this he obviously has succeeded.

We find the contents classified in 5 sections and 28 chapters; part I, discussing the nature of inorganic and organic body constituents, as salts, carbohydrates and proteins, part II, recording elaborate tabulations of the composition of body tissues, part III, mentioning essential food constituents as elements, protein requirements and vitamins, including the new blood-clotting vitamin K, part IV, enumerating mechanisms and agents effecting chemical changes in the body, as enzymes and hormones, part V, elaborating on metabolic processes and chemotherapy.

The discussion of chemotherapy probably is of special interest to the pharmaceutical chemist. Williams presents a very brief but stimulating and in some respects critical survey. Thus the author writes: "That such a simple compound (carbon tetrachloride in the treatment of hookworm) is valuable illustrates the fact that simple compounds are likely to be overlooked and that no one can tell in advance from what source a valuable therapeutic agent may come". Of significance is also this statement: "The discovery of sulfanilamide as a chemotherapeutic agent is considered by many to be the outstanding advance in the whole field of medicine in recent years.

"Since the compound sulfanilamide has been known to chemists for about thirty years and the bacterial infections for which it has been found to be a specific, have likewise been known for several decades one cannot help but suspect that there may be lying at hand in the organic chemistry laboratories other chemotherapeutical agents

of great value, which are undiscovered because suitable trials have not been made. A vast field of experimentation lies ahead for competent and well trained investigators."

A helpful glossary of physiological and medical terms concludes the book, which we feel deserves to become a popular guide to students of this special field of medical biochemistry.

ARNO VIEHOEVER.

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**A Textbook of Physiology.** William D. Zoethout, Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). 6th edition, 1938. C. V. Mosby Co., St. Louis. Price: $4.00.

It is said that when the King of England asked Faraday what was the practical value of all his investigations into magnetic currents the scientist replied, "What is the use of a baby?" Few persons today will question the value of research in what we call "abstract science," that is the pursuit of knowledge simply for the sake of knowing. An accumulation of already discovered facts in any realm of science is of value (1) as a source of mental satisfaction, (2) as a starting point for new research, and (3) because of their possible practical applications. For pharmacists it would seem that there is scarcely any branch of science which should bring more rewards for all three reasons than physiology.

For the pharmacist who would like a deeper acquaintance with the facts of physiology than that which he acquired as a student (many of which he has probably forgotten) we can heartily recommend this book which, while less elaborate than several available works on the subject, is considerably more advanced than the type of book commonly used in colleges of pharmacy and gives an unusually clear insight into the philosophy of this science. Professor Zoethout is to be especially commended for the clarity of his exposition, which is due chiefly to three things: his avoidance of unnecessary polysyllabic technical slang, the space devoted to explanation of the newer phenomena of related sciences (for example, fifteen pages are given to a summary of the basic principles of osmosis which are fundamental to an understanding of all cellular activity) and to the numerous (291) well-chosen illustrations. That we are not alone in our appreciation of this work is evidenced by the fact that the book has passed through five editions in twelve years.

H. C. WOOD, JR.

**The Chemistry of the Sterids.** Harry Sobotka. The Williams and Wilkins Co., Baltimore, 1938. 634 pages.

This book is a comprehensive treatment of the chemistry of sterols and related compounds, grouped together as the sterids. The longest known representatives of this class of natural products are the sterols (cholesterol, ergosterol, etc.) and the bile acids. More recently it has been shown that to this group belong also several of the sex hormones, antirachitic vitamins and carcinogenic agents. The important class of cardiac glycosides and the related saponins have been recently identified as derivatives of the same essential structure.

The first chapter deals with the history of sterid chemistry, which is almost exclusively associated with investigations of bile and its constituents. The author then goes on to discuss the methods which have been used in structural research on the sterids. Together with this discussion is a comprehensive description of chemical and physical properties of the numerous derivatives and degradation products obtained by laboratory research on the naturally occurring sterids. This is followed by a chapter dealing with steric considerations; the complex structure of the sterids, comprising several ring systems, leads to the possibility of the existence of many isomeric substances. The methods employed in determining the configurations of these isomers are discussed.

A chapter is devoted to the chemical properties of conjugated and free bile acids; another to the chemistry of the other sterids. Molecular (co-ordination) compounds of the sterids are discussed in detail. Analytical methods used in the estimation of sterids in natural products are discussed. Following this is an extensive classified catalog of all sterids and their derivatives, containing their structural formulæ, various physical constants, their occurrence, formation, and synthesis, together with chemical reactions and transformations. This catalog is complete, from all available sources, to January, 1937. A complete bibliography and author index is appended; a subject index completes the work.

This volume is a highly commendable, authoritative compilation of the available data on the chemistry of the sterids. It serves to bring together, in well-planned style, the voluminous literature on this important subject. Publications have accumulated, in widely scattered places, and this is the first attempt to collect and catalog the facts relative to this important field. The book will undoubtedly meet with the enthusiastic reception it merits from workers in the field of sterid chemistry.

L. A. R.